Aspirin-Induced Prolongation of the Ivy Bleeding Time

Its Diagnostic Usefulness

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■ *Ivy bleeding time values before and two hours after ingestion of 600 mg of aspirin (aspirin tolerance test) were studied in normal persons, in patients with a disorder of primary hemostasis and in patients with various coagulation factor deficiencies. Aspirin produced a significant prolongation of the bleeding time in patients with von Willebrand's disease, uremia, and primary platelet disease, and in two patients with Factor XI deficiency. Dextropropoxyphene hydrochloride caused no prolongation of the bleeding time in normal persons.*

INGESTION OF ACETYLSALICYLIC acid (aspirin, A.S.A.) prolongs the bleeding time in normal persons.[1-6] The degree of prolongation varies with the bleeding time technique used (Duke,[7] Ivy,[8] or Borchgrevink[9]), the dosage of the drug given,[10] and the time between the ingestion of drug and the performance of the test. The mechanism responsible for prolongation of the bleeding time after aspirin ingestion appears related to the ability of this drug to impair platelet release of adenosine diphosphate.[11]

The present study was undertaken to define precisely the limits of prolongation of the Ivy bleeding time in normal persons exactly two hours after ingestion of 600 mg aspirin (the aspirin tolerance test). The aspirin tolerance test was also performed on patients with von Willebrand's disease, uremia, primary platelet disease, or a congenital coagulation factor deficiency other than Factors VIII or IX. In addition, the effect of dextropropoxyphene hydrochloride on the bleeding time of normal persons was investigated.

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Materials and Methods

The bleeding time was measured before and exactly two hours after ingestion of aspirin (acetylsalicylic acid, N.F.), 600 mg, in 44 normal persons with no evidence of a hematologic abnormality, in five patients with von Willebrand's disease, in ten patients with uremia (six of whom were undergoing chronic hemodialysis), in seven patients with well documented primary platelet disease,[12] and in seven patients with Factor V, VII, XI, or XII deficiency. Primary platelet disease refers specifically to a familial bleeding disorder in which the principal char-

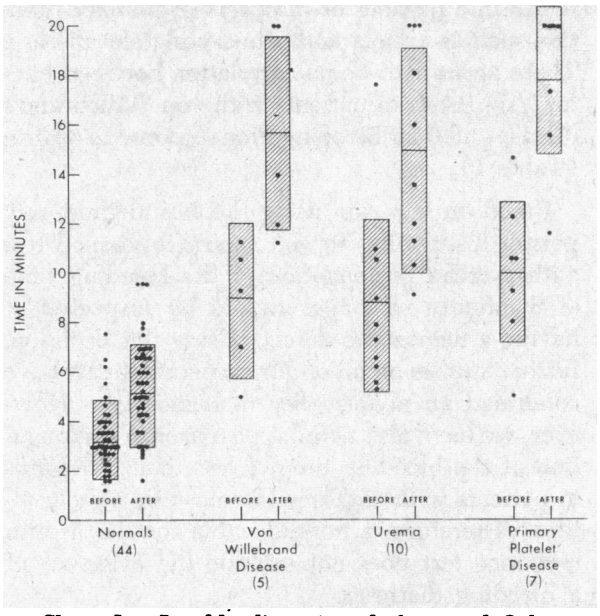

Chart 1.—Ivy bleeding time before and 2 hours after ingestion of 600 mg of aspirin in normal controls and in patients with hemostatic disorders. Each dot represents the mean of three bleeding time incisions. The shaded column represents ± 1 S.D. and the horizontal bar, the mean for that group.

acteristic is defective collagen-induced and epinephrine-induced platelet aggregation but normal clot retraction and factor VIII levels. In 19 of the 44 normal controls, the bleeding time was also measured before and two hours after administration of 65 mg of dextropropoxyphene hydrochloride. Bleeding time was measured by the method of Ivy.[13] Three incisions, 5 mm deep and 2 mm wide, were made in the volar aspect of the forearm with a spring-loaded lancet,[14] using an ASR Sterisharp No. 11 scalpel blade.* Standardization of the incision may be assured by a 5 mm deep incision with any brand of No. 11 blade since such a technique conveniently produces an incision width of exactly 2 mm without need for further lateral movement. The mean (± 1 S.D.) bleeding time for the three incisions was determined; any single bleeding time greater than 20 minutes was scored as 20 minutes. Measurements were carried out at random by four hematologists. Data were analyzed by Student's *t*-test.

Results

In 44 normal controls, mean bleeding time increased significantly ($P < .001$) from 3.2 ± 1.5 minutes before aspirin ingestion to 4.9 ± 2.0 minutes after aspirin ingestion (Chart 1); the mean prolongation was 1.7 minutes. In the ten patients with uremia (two of whom had mild thrombocytopenia, 121,000 and 124,000 platelets per cu mm) mean bleeding time also increased significantly ($P < .01$) from 8.8 ± 3.8 to 15.0 ± 4.4 minutes after aspirin ingestion (Chart 1). In the patients with either von Willebrand's disease or primary platelet disease the bleeding times were, respectively, 8.7 ± 3.5 and 10.1 ± 3.3 minutes before aspirin and 15.6 ± 4.6 and 17.7 ± 3.4 minutes after aspirin, and these proved to be highly significant in both groups ($P < .01$). In the five patients with von Willebrand's disease, there was no relationship between the degree of prolongation of the bleeding time and Factor VIII levels (Table 1). The mean bleeding time for all 22 patients with a hemostatic disorder increased significantly ($P < .001$) from 9.8 ± 3.8 minutes before aspirin ingestion to 16.2 ± 3.6 minutes after aspirin; the mean prolongation of the bleeding time was 6.7 minutes. Prolongation of the bleeding time after aspirin in patients with a coagulation factor deficiency is shown in Chart 2. The only significant prolongation of bleeding time—that is, 7 and 8 minutes—occurred in the two patients with Factor XI deficiency. (Factor XI quantitative assay <1 percent and 3 percent respectively.[15]) Dextropropoxyphene hydrochloride had no effect on the bleeding time in any of the 19 normal persons tested (3.2 ± 1.2 minutes before and 3.4 ± 1.4 minutes after aspirin). No significant difference was found between the results of two and three bleeding time incisions, regardless of whether the subject was normal or abnormal or whether or not aspirin had been ingested.

TABLE 1.—*Ivy Bleeding Time and Factor VIII Levels Before and After the Aspirin Tolerance Test in Five Patients with Von Willebrand's Disease*

	Before Aspirin Ingestion		*After Aspirin Ingestion**	
Patient	*Mean Bleeding Time (minutes)*	*Factor VIII Level (%)*	*Mean Bleeding Time (minutes)*	*Mean Prolongation of Bleeding Time (minutes)*
A	11.3	30	14	2.7
B	5.0	33	11.3	6.3
C	10.7	2	20	9.3
D	7.0	7.4	12	5.0
E	9.3	45	20	10.7

*600 mg orally.

*The dimensions of the first 10 mm of any commercially available No. 11 scalpel blade are exactly the same as those of a Bard Parker No. 11 blade.

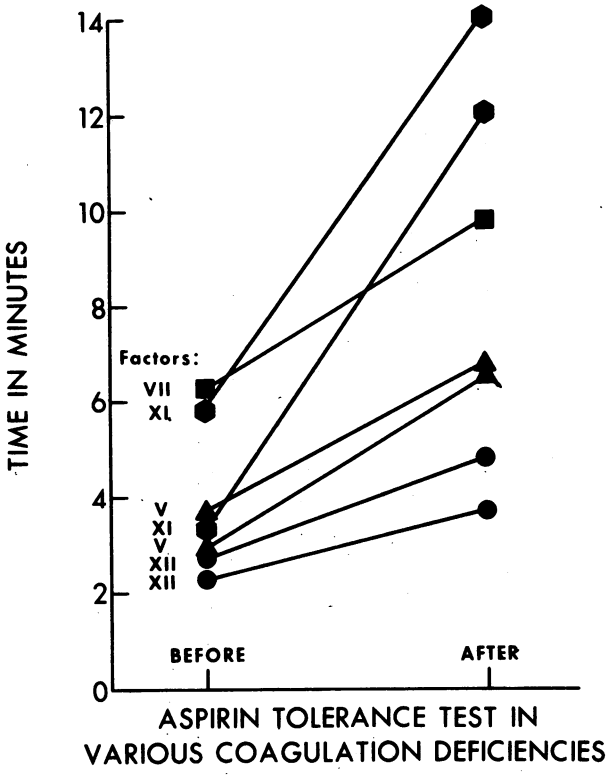

Chart 2.—Ivy bleeding time before and 2 hours after ingestion of 600 mg of aspirin in seven patients with severe congenital coagulation factor deficiencies.

Discussion

The results indicate that the aspirin tolerance test can be standardized for use as a diagnostic procedure for the detection of hemostatic dysfunction. This test caused a mean prolongation of the Ivy bleeding time of 1.7 minutes in normal persons, and only one had a prolongation of greater than 4 minutes (5.3 minutes). These results contrast sharply with the mean bleeding time prolongation of 6.7 minutes produced by the aspirin tolerance test in the 22 patients with disorders of primary hemostasis.

Quick has stressed the value of the aspirin tolerance test in detecting von Willebrand's disease by prolonging the Duke bleeding time of those patients initially presenting with normal or borderline bleeding time.[3,16] The severe prolongation of the bleeding time he observed using the Duke technique has not been observed consistently by other investigators using the Ivy technique.[4,17] It is important to recognize that an abnormal result in the aspirin tolerance test is not specific for von Willebrand's disease, as it is found in a number of disorders of platelet function such as uremia and primary platelet disease. There appears to be no correlation between Factor VIII levels in patients with von Willebrand's disease and their bleeding time response to aspirin (Table 1).

Based on our data using the Ivy method, any person responding to the aspirin tolerance test with a mean prolongation of the bleeding time of 6 minutes or longer should be suspected of having a hemostatic defect. Using this criterion, further studies on all of our suspect patients have confirmed an abnormality in hemostasis. However, we have also noted a post-aspirin prolongation of the bleeding time of less than 6 minutes in patients with confirmed hemostatic abnormalities. Therefore, a normal value for the aspirin tolerance test does not exclude the existence of a bleeding diathesis.

Aspirin was first noted to have an adverse effect on the Duke bleeding time in patients with hemophilia in 1955.[1] In 1967, Quick[16] observed that a profound prolongation of the bleeding time occurred after aspirin ingestion in patients with either hemophilia A or B and suggested that aspirin might enhance the bleeding potential of these patients. Kaneshiro et al[17] also observed prolongation of the Ivy bleeding time after aspirin in some but not all patients with severe hemophilia A or B, and noted a normal response to the aspirin tolerance test in patients with mild hemophilia. Our limited studies of patients with severe congenital deficiency of Factors V, VII, XI or XII seem to indicate that Factor XI deficiency is associated with an abnormal bleeding time response to aspirin. It should be noted that several observers[18,19,20] have reported an unusual condition in which a long bleeding time has been associated with factor XI deficiency apparently unrelated to aspirin ingestion. However, Kaneshiro et al found no post-aspirin bleeding time abnormality in three patients with Factor XI deficiency. Perhaps these contrasting findings are related to the differences in the bleeding time technique used. Quick[21] reported that two patients with Factor II deficiency and two with Factor VII deficiency had a bleeding time prolongation after aspirin but the results are difficult to interpret since the length of post-aspirin prolongation for normal subjects was not defined.

It is clear from the pronounced prolongation of bleeding time produced by aspirin in patients

with von Willebrand's disease, uremia or primary platelet disease why this medication is potentially dangerous in any patient with defective hemostasis. One uremic subject in this study bled heavily from the bleeding time incision sites after aspirin ingestion and required blood transfusions before the bleeding problem was controlled. Any patient with an abnormal response to the aspirin tolerance test as defined herein should be observed for subsequent bleeding complications. The lack of effect of dextropropoxyphene hydrochloride on the bleeding time of the normal subjects we studied suggests that this drug is safe for use in patients with hemostatic disorders who require oral analgesics. Acetaminophen has also been shown to have no untoward effect on the Ivy bleeding time in normal subjects.[22]

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